Translation from Chinese
REf. #1-36/wb

(BJ) Number 1456

[19] Patent Office of the People's Republic of China

[11] Issue Number: CN 1079391A

[12] Public Explanation of Patent Application for Invention

[21] Application Number: 92104358.9

[43] Date of Publication: December 15, 1993

[51] Int.Cl^{6} A61K 35/78

[22] Date of Application: May 31, 1992

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A61K 33/36 A61K 9/127

No. of Pages in Explanations: 6 No. of Pages of Attached Drawings:

[54] Name of Invention: Method for the Preparation of Directly Administered Arsenic Preparations Used for the Focus of Cancer

[57] Abstract

This invention is a method for the preparation of [redacted] for the focus of [redacted] It is a preparation technique for an anticarcinogenic pharmaceutical preparation which applies modern technology to make it into a specified dosage form. The aim is to introduce the therapeutic effects of the above mentioned arsenic preparation against [redacted] and at the same time a method for the preparation of an arsenic preparation is also presented which can be used for the treatment of [redacted] Moreover, owing to the fact that a special processing method was adopted for the inner, middle and outer layers of the liposomes, the preparation method for liposomes given in this invention is not only suitable for industrialized, mass production, but it has also resolved the difficulties of the storage time of liposome wet products being short and easily leaking; the dry products easily have adhesion and absorbed moisture, and after deliquescence, it is easy to have rancidity degeneracy. It is necessary to carry out extrusion filtering, homogenization, etc. when there is redissolution of dry product liposomes.

Claims

1. The special characteristic of the method for the preparation of directly administered arsenic preparations for the focus of cancer is the use of oxide with trivalent arsenic, salt, organic compounds, and at least one type of simple or compound traditional Chinese medicine recipe as the raw materials, combination with specified auxiliary materials, and processing into ointment, paste, suspended injection, liposomes, etc. with trivalent arsenic.

2. The special characteristic of the ointment and paste described in Claim 1 is that at least two types from among oils, lipoids, hydrocarbon, silicone, zinc oxide, and starch can be used for the base material. A phospholipid can be used for one of these so as to increase the affinity between the medicine and focus, the arsenic content is calculated with arsenic trioxide, and it should be controlled between 0.1%-10%.

3. The special characteristic of the suspended injection described in Claim 1 is that at least one type from among vegetable oil, benzyl formate, and ethyl oleate can be used for the solvent, at least one type from among aluminum monostearate, aluminum distearate and aluminum tristearate is used for the suspension agent, the dosage ratio of the suspension agent and solvent is 0.5:100-5:100, the arsenic contents are measured using arsenic trioxide, and it should be controlled between 0.01%-5%.

4. The special characteristic of the liposome described in Claim 1 is that its method of preparation is similar to that of the preparation of W/O/W compound emulsion, that is, after oil containing surface active agent

combines with water and emulsifies into W/O emulsion, this emulsion is then mixed into water containing surface active agent and emulsified into W/O/W compound emulsion. It is necessary in different places during the preparation of the liposomes to evaporate out the major portion of the oil phase for the W/O emulsion changing it into a thick emulsion, and then preparing W/O/W emulsion. Moreover, there is simultaneous spray drying of this W/O/W emulsion and high viscosity polymer liquid, that is, the dried surface forms liposome particles with a layer of polymer film.

5. The special characteristic of the phase aqueous solution in the liposome described in Claim 4 is that it prevents the drug from precipitating arsenic trioxide which does not dissolve in water and leaking out from the liposome layer. The aqueous phase is adjusted to pH 8-10 with alkaline buffer solution, and sodium bicarbonate, sodium hydroxide, potassium hydrogen carbonate, sodium hydrogen phosphate, potassium phosphate, etc. can be used for the buffer.

6. The special characteristic of the preparation method for the liposome described in Claim 4 is that there are at least two types from among phosphatidyl cholin 1.e, phosphatidyl glycerol, lecithin choline, legume phosphatidyl choline, hydrogenated legume phosphatidyl choline, palmityl phosphatidyl choline, distearyl phosphatidyl choline, dimyristol phosphatidyl choline, dispermaceti phosphatidyl choline, sulfolipid, cholesterol, coprosterol, cholestanol, %-tocopherol, half succinic acid cholesterol, etc. which can be used for the liposome double layer molecular layer material. Its total dosage is equivalent to 0.5-15% of the liposome solution prior to spray drying, the ratio of the inner and outer layer lipid

is approximately 1:2, the ratio of the phospholipid and cholesterol should be between 1:0.2-1:1, and the ratio of the cholesterol in the inner phospholipid layer should be greater than that of the outer layer.

7. The special characteristic of the preparation method for the liposome described in Claim 4 is that an oil gel phase is lastly formed between the double molecular layer of the liposome. The oil gel layer can be formed through the selection of one from among axunge or vegetable oil, benzyl formate, ethyl oleate and the suspension agents aluminum monostearate, aluminum distearate and aluminum tristearate. The ratio of the amount of axunge or oil gel and the liposome double molecular layer material should be between 0-500%. The ratio of the suspension agent in the oil gel and the oil phase should be between 0.5-5%.

8. The special characteristic of the preparation method for the liposome described in Claim 4 is that sodium alginate, methyl cellulose, carboxymethyl cellulose, polyvinyl pyrrolidone, etc. can be used for the high viscosity polymer spray dried at the same time as the liposome. The dosage should be determined based on the slow release level required by the different types of polymers and the liposomes in the cancer entity after redissolution. The spray drying method carries out spray drying after the even mixture of this high viscosity polymer liquid and the liposome. The method of using two different sprays from different spray guns for simultaneous or intermittent spraying can also be employed.

Explanations

Method for the Preparation of Directly Administered Arsenic Preparations Used for the Focus of Cancer

This invention involves the technique for an anticarcinogenic drug preparation.

The direct administration of traditional Chinese medicine simple and compound recipes of arsenic for the focus of cancer has already been widely used without any special instruments for the direct treatment of body surface and cavity cancerous tumors, and eye-catching therapeutic effects have been attained. The "Collection of Materials on New Medical Methods Using Chinese Herbal Medicine" from Liaoning records that the [redacted] 2 qian of white arsenic and 2 liang of wheatmeal) [redacted] Li Changbei of the Uighur Autonomous County Hospital in Meng Cun, Hebei Province used "Wu Yan Dan" (baliary calculus, magnetite, cinnabar, alum, and realgar [redacted]) to treat 16 cases of [redacted] 10 cases were cured, 6 cases showed improvement, and the effective rate was 100%. Yang Xuezhi and others of the Cervical Cancer Laboratory of the Obstetrical and Gynecology Institute of the Jiangxi Provincial Women's Health Care Hospital used the "three grades of medicine" of traditional Chinese medicine, medicinal cakes and rod [redacted], white alum, realgar, and myrrha) [redacted] They carried out strict, periodic follow-up surveys and reexaminations on the therapeutic effects on all of the patients: aside from 1 case that died from chronic nephritic uremia after 3 years and 1 case that died from cerebral hemorrhaging after 4.5 years, the other 188 cases were all

healthy (follow-up surveys were carried out during different years between 1972-1982), and no reoccurences were seen. The cure rate was 100%. Moreover, the 1977 edition of "Drug Standards of Henan Province" records "Pi Ai Jing" (arsenolite, finger nails, hair, Fructus Ziziphi Jujubae, alkali leavened dough - this prescription can also be viewed as an arsenolite simple recipe, the other ingredients can all be regarded as slow releasing agents). The therapeutic effects of the above mentioned simple and compound [redacted] cancer. However, their range of application is quite narrow, and they are still unable to touch upon in vivo cancer tumors. At the same time, when using the drug for the body surface and cavities, it is somewhat weak in terms of dosage forms. Some of the dosage forms are not advantageous to industrialized mass production, some are not convenient to use, and for some it is difficult to control the quality between batches during production.

The task of this invention is to also be able, given that traditional Chinese medicine simple and compound recipes are not excluded, to individually use [redacted] the raw material to make specified dosage forms, introduce the therapeutic effects of the above mentioned arsenic preparation on body surface and cavity tumors into the body, and at the same time also give a method for the industrialized mass production of a preparation to treat body surface and cavity tumors.

The arsenic preparation of this invention mainly uses trivalent arsenic oxides (equivalent to single recipe arsenolite), salts, organic compounds, and their compound recipe traditional Chinese medicines as the raw material, it

is matched and processed with a specified carrier, and then made into an ointment (I) and paste (II) used for body surface and cavity tumors as well as a [redacted]

The preparation method for (I) and (II) is: after the drug (at least one type can be used from among the trivalent arsenic oxides, salts, organic compounds, and compound recipe traditional Chinese medicine) and the base material (at least one type can be used from among oils, lipoids, hydrocarbon, starch, zinc oxide, and silicone) are separately preprocessed, the sequence of each type of base material proceeds from high to low based on the melting point, they are successively added in and fused, and then prepared for use after being mixed evenly. After the drug and small amount of fused base material are mixed evenly, it is duplicated and diluted with the other base materials, and mixed evenly until there is a sense of there no longer being any grains.

The preparation method for (III) is: after the drug (at least one type can be used from among the [redacted] and compound recipe traditional Chinese medicine), the solvent (vegetable oil, benzyl formate, and ethyl oleate can be selected), and the [redacted] (aluminum monostearate, aluminum distearate and aluminum tristearate can be selected) are separately preprocessed, the suspension agent is dissolved in the solvent and forms an oil gel. Afterwards, [redacted]

The preparation method for (IV) is: after the drug (at least one type can be used from among the [redacted]

[redacted] and compound recipe traditional Chinese medicine), pH buffer agent of the internal aqueous solution (sodium bicarbonate, potassium hydrogen carbonate, sodium hydroxide, sodium hydrogen phosphate, and potassium phosphate can be selected), oil phase (at least one type from among axunge, vegetable oil, benzyl formate, ethyl oleate, and chloroform), suspension agent (aluminum monostearate, aluminum distearate and aluminum tristearate, etc. can be selected), liposome material (at least two types from among phosphatidyl choline, phosphatidyl glycerol, lecithin choline, hydrogenated legume phosphatidyl choline, palmityl phosphatidyl choline, distearyl phosphatidyl choline, dimyristol phosphatidyl choline, dispermaceti phosphatidyl choline, legume phosphatidyl choline, sulfolipid, cholesterol, coprosterol, cholestanol, %-tocopherol, etc. can be selected), spray drying anticoagulant, and entity injection time-releasing agent (sodium alginate, methyl cellulose, carboxymethyl cellulose, polyvinyl pyrrolidone, etc.) are preprocessed, they are prepared for use. The drug is dissolved in the inner layer aqueous phase buffer solution, the pH is adjusted to 8-10, and it is prepared for use. The suspension agent, 1/3 of the phospholipid and cholesterol are separately dissolved in the oil phase. Afterwards, the above mentioned buffer solution containing the drug is added while mixing into the oil phase to carry out emulsification, and a concentrated W/O emulsion is formed. This concentrated emulsion is added while mixing into the aqueous solution containing the total 2/3 of the phospholipid and cholesterol, and it forms the W/O/W compound emulsion. After homogenization, spray drying of this emulsion is carried out simultaneously with the high viscosity polymer solution, that is, it is able to form liposome particles with a polymer film layer on the surface.

The advantages of this invention are that, when compared with the traditional administered dosage form, the application range is more extensive, the dosage is more exact, the orientation is better, and it is more suitable to industrialized mass production; the total administered dosage is less than that for systemically administered drugs, the concentration of focus entity drugs is high, the therapeutic effects are high, results are seen quickly, and the side effects are small. Moreover, the liposome preparation method presented by this invention is not only suitable to industrialized mass production, but it has also resolved the problems of the storage of wet liposome products being short, easily leaking, the dry products easily having adhesion and absorbing moisture, it is easy to have rancidity degeneracy after deliquescence, and it is necessary to carry out extrusion filtering, homogenization, etc. when water is added and there is redissolution during usage.

The prescription and technical examples are:

Example 1-2

Component:	(I)	(II)
"Three grades of medicines"	100g	250g
White vaseline	800g	420g
Lanolin	50g	50g
Lecithin	30g	30g
Zinc oxide	20g	100g
Starch		150g

Technique: the "three grades of medicines" were prepared, we pulverized through a 200 mesh sieve, mixed

evenly with the zinc oxide and starch, and prepared for use after successively adding in lecithin based on melting point proceeding from high to low, melted, and mixed. After grinding evenly the mixture of the above mentioned drug and the small amount of melted base material, we then mixed it evenly with the duplicated dilution of the remaining base material until there was no longer any sense of grains.

Example 3 Prescription:

Component:	(III)
"Three grades of medicines"	50g
Aluminum monostearate	20g
Neutral peanut oil	Add to 1000ml

Technique: the "three grades of medicines" were prepared, we carried out comminution by gas stream, took the neutral peanut oil which had been filtered and sterilized, combined with the oil immersed aluminum monostearate to make an 8% oil gel, heated to 120°C, maintained the temperature for 1 hour, diluted into a 2% oil gel, mixed evenly and prepared for use. The drug powder was completely mixed with this oil gel, and then the colloid was used to grind it fine to standard.

Example 4 The prescription of (IV): 10g of arsenic trioxide, the inner phase used 40g of distilled water, 7g of potassium hydrogen carbonate, 20g of neutral bean oil, 0.4g of aluminum monostearate, 80g of chloroform, the inner layer used 8g (1:0.8 g molecular ratio) of hydrogenated soybean phospholipid/cholesterol, the outer phase used 400g of distilled water, the outer layer used 16g (1:0.6 molecular ratio) of hydrogenated soybean phospholipid/cholesterol, and 500g of water as well as 5g of methyl cellulose were used

for the spray anticoagulant. The technique of (IV): we dissolved the arsenic trioxide into 40ml of water containing potassium hydrogen carbonate, and adjusted pH to 8 to form aqueous phase. 8g of phospholipid/cholesterol were dissolved in chloroform and prepared for use. The neutral bean oil and aluminum monostearate were made into a 2% oil gel in accordance with the method given in Example 3. It was diluted into the above mentioned chloroform solution and formed an oil phase. We added the aqueous phase into the oil phase, and homogenized with a homogenizer. We obtained the W/O emulsion, vaporized out 55-70% of this emulsion under 40°C decompression conditions, obtained the concentrated W/O emulsion, added this concentrated emulsion into an aqueous solution containing phospholipid/cholesterol while stirring, emulsified, and formed the W/O/W compound emulsion. At this time, we mixed this W/O/W compound emulsion with the solution containing methyl cellulose evenly, and immediately spray dried. We were then able to obtain liposome particles with a layer of methyl cellulose film, and separately packaged.

Notes:

1. The adding of a minute amount of oil gel between the double molecular layers of the liposomes can effectively prevent the leaking of the inner layer soluble drug.

2. Injection of the arsenic trioxide cancer entity. The adding of the thickener and time-releasing agent in (III) and (IV) can stop the leaking of the drug from the cancer entity, and it does not have any negative effects on the human body. Owing to the fact that a small dosage of the Fowler solution (potassium arsenite solution) is a roborant, it is also a commonly used oral medication.*

3. The redissolution method for the liposome particles with methyl cellulose film is: a fixed quantity of distilled water is heated to 50°C and poured into an ampul containing liposomes, we continually shook it, waited until the temperature decreased to room temperature (it is best to be 5°C), and then the particles are suspended and dispersed evenly.

*Medicine and Pharmacology Science and Technology Press of China, August 1989, "Drug Structures and Preparations," p. 30.